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Multinomial model-based formulations of TCP and NTCP for radiotherapy treatment planning

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Abstract

Hit and target models of tumour growth, typically assume that all surviving cells have a constant and homogeneous sensitivity during the radiotherapy period. In this study, we propose a new multinomial model based on a discrete-time Markov chain, able to take into account cell repair, cell damage heterogeneity and cell proliferation. The proposed model relies on the 'Hit paradigm' and 'Target' theory in radiobiology and assumes that a cancer cell contains m targets which must be all deactivated to produce cell death. The surviving cell population is then split up into m categories to introduce the variation of cancer cell radio-sensitivity according to their damage states. New expressions of the tumour control probability (TCP) and normal tissue complication probability (NTCP) are provided. Moreover, we show that hit and target models may be regarded as particular cases of the multinomial model. Numerical results should permit to keep the efficiency of treatment with a lower total radiation dose than that given by the typical hit models, which allows to decrease side effects.

Key words: Markov chain, multinomial model, tumor growth, radiotherapy

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Introduction

The aim of radiotherapy is to deliver enough radiation to the tumour to control it without irradiating normal tissue to a dose that will lead to serious complications (morbidity). Since radiation delivery at a precise point of cells is generally described as a random variable, the effects of the radioactive treatments on cancer and healthy cells are characterized by two probabilities: (i) the Tumour Control Probability (TCP) and (ii) the Normal Tissue Complication Probability (NTCP)³⁻⁵. The optimum choice of radiation dose delivery technique in the treatment of a given tumour has to maximize the TCP so that at the same time the NTCP must be lower than an acceptable level. The model-based probabilities TCP and NTCP are then used to choose the 'best' treatment plan. Since Holthusen in⁶, TCP and NTCP dose functions have been used to determine the 'optimal' dose to be delivered by maximizing biological objective functions like $TCP(1 - NTCP)$. An evolution of this objective function is proposed in⁷. In clinical radiotherapy a typical choice is $TCP \geq 0.5$ and $NTCP \leq 0.05$ ⁸. Expressions for TCP and NTCP can be derived using survival curves⁹, stochastic cell population-dynamic models^{10,11} or cell-cycle models¹². Here, we focus on a popular class of models used in radiotherapy, *i.e.* the hit models coming from target theory.

Target theory and *hit-modeling paradigm* were introduced in the 1920s when biologists were beginning to develop quantum approaches to inactivation phenomena in irradiated biological tissue¹³⁻¹⁵. The modeling of radiation effects on living cells were continued both theoretically and experimentally by K. C. Atwood and A. Norman¹⁶, D. E. Lea¹⁷, E. C. Pollard and coworkers^{18,19}. Since these seminal works, a lot of mathematical models expressing the interaction

of radiation particles with biological cells have been proposed^{20–25}. In target theory, a cell has different vital sites called targets which must be inactivated to kill the cell. For instance, it is accepted that the chromosomes are sensitive targets²⁶ but there is additional evidence that the nuclear membrane, or some cell organelles close to the nuclear membrane can also be regarded as targets²⁷. Each target is deactivated when it is hit by a number of radiation particules. There are several classes of hit models classified by the number of targets and the number of hits. In these models, it is generally assumed that cells have homogeneous behaviour. In practice, there are at least three main reasons to put this hypothesis into question. The first cause of heterogeneity comes from the nonuniform spatial distribution of the radiation dose. The second cause is due to the differences between the cell types (necrotic, quiescent, proliferating, stem cells, etc.) and the nonuniform concentration of oxygen and nutrients. A third factor corresponds to a cell-to-cell variability of damages and to the variation of the cell sensitivity to radiation. The first two points may be handled by reducing the modeling scale to a voxel level, *i.e.* a sub-volume in which we can reasonably suppose that distribution doses and cell types are homogeneous. For the last point, the hit models typically assume that cell sensitivity to radiation is constant over the time course of radiotherapy. In other words, after a radiation dose, a surviving cell is thought to be about as viable as an unirradiated cell and all cells are supposed having the same survival probability. However, evidence suggests that the cell radiation sensitivity increases with the number of dose fraction and even the cell is still alive, it partially loses the ability to resist as an unirradiated cell. Our aim is to focus on this last issue and a triple objective is addressed:

- to propose an extension of hit models based on a Markov chain formalism

able to describe the target reparation between two consecutive dose fractions of the radiation schedule, the heterogeneity of damages induced by radiations and the cell proliferation;

- to determine the TCP and NTCP;
- through numerical computations, we compare the multinomial model with typical hit models and we draw the optimal total dose from the TCP/NTCP curves.

This paper is structured as follows: we present a brief overview of hit models and target theory in Section 1. We give a detailed development of the tumour growth *multinomial* model in Section 2. In Section 3 we review existing classical TCP models. Based on the *multinomial* model, we propose a new expression of TCP in Section 3 and NTCP in Section 4. **In Section 5, we integrate the cell proliferation into our approach.** Numerical results are presented in Section 6. Finally, the main results, limits and perspectives of the multinomial model are drawn in Section 7.

1 Radiation, hit models and target theory

The main notations used thereafter are presented in Table 1.

1.1 Hit process

For a radiation dose u_0 , the number of delivered radiation particles is

$$n_p = u_0 \rho, \tag{1.1}$$

Table 1
Main notations

Notations	
Not.	Definition
k	discrete time
n_p	number of delivered radiation particles per a radiation dose u_0
q_h	probability that a radiation particle hits a target
N_h	number of radiation particles that hit a critical target
q_c	probability of cell death after radiation
p_c	survival probability of a cell after treatment
v	voxel (subvolume) of a 3-D scan
Z_k	number of deactivated targets in the cell
Π	transition matrix associated with the Markov chain (Z_k)
\mathbf{P}	matrix associated with treatment effects
\mathbf{R}	matrix associated with cell repair process
$X_{k,v}(i)$	number of cancer cells in state i in the voxel v at time k
$\bar{X}_{k,v}(i)$	number of normal cells in state i in the voxel v at time k
m	number of targets in a cancer cell
q	probability to deactivate a target in a cancer cell
r	probability for an inactivated target to be reactivated in a cancer cell
n_0	initial total number of cancer cells in the tumour
n_t	total number of tumour voxels
n_v	initial number of cancer cells in a tumour voxel v
\bar{m}	number of targets in a normal cell
\bar{q}	probability to deactivate a target in a normal cell
\bar{r}	probability for an inactive target to be reactivated in a normal cell
\bar{n}_0	initial total number of normal cells in the irradiated zone
\bar{n}_t	total number of normal tissue voxels
\bar{n}_v	initial number of cells in a normal tissue voxel v
\bar{n}	the complication threshold number of dead normal cells

with ρ the number of radiation particles per unit dose and the subscript p corresponds to particles. Thereafter, n_p is assumed to be an integer for simplification. The underlying assumptions²³ of the hit models are:

- (1) a cell has at least one critical target;
- (2) the probability q_h (the subscript h corresponds to hit) that a radiation particle hits a critical target is the same for all targets;
- (3) the hit events are independent from each other.

Let N_h be the random variable denoting the number of radiation particles that hit a given target. Then, $N_h \sim \mathcal{B}(n_p, q_h)$ (binomial distribution) and the probability that exactly j radiation particles hit a given critical target is:

$$Pr(N_h = j) = \binom{n_p}{j} q_h^j (1 - q_h)^{n_p - j}, \quad j = 0, 1, 2, \dots, n_p. \quad (1.2)$$

If n_p is large enough and q_h is low, such as $n_p q_h = \lambda \in [0, 10]$, the distribution of N_h can be approximated by the Poisson distribution $\mathcal{P}(\lambda)$. Fixing

$$\alpha = \rho q_h, \quad (1.3)$$

then according to (1.1), $\lambda = n_p q_h = \alpha u_0$ and the probability that exactly j radiation particles hit a target becomes

$$Pr(N_h = j) = \frac{(\alpha u_0)^j}{j!} e^{-\alpha u_0}, \quad j = 0, 1, 2, \dots \quad (1.4)$$

αu_0 is the expected number of primary lesions caused by the radiation dose u_0 and the parameter α can be interpreted as a characteristic of the damage process itself, *i.e.* radiosensitivity in its literal sense²⁸. There are several classes of hit models classified by the numbers of targets and hits.

1.2 Single target–single-hit models

In *single target–single-hit models*, it is assumed that a cell has one lethal target and that the cell dies when its target is hit by one or more radiation particles. Therefore, the cell dies with probability

$$q_c := P(N_h \geq 1) = 1 - e^{-\alpha u_0}. \quad (1.5)$$

1.3 Single target–multi-hit models

In *single target–multi-hit models*, the cell dies when the target is hit by at least h_t radiation particles, where h_t is a threshold number of cell inactivations also called *extrapolation number*. Therefore, the probability that the cell dies is

$$q_c := P(N_h \geq h_t) = \sum_{j=h_t}^{\infty} \frac{(\alpha u_0)^j}{j!} e^{-\alpha u_0} = 1 - e^{-\alpha u_0} - \dots - \frac{(\alpha u_0)^{h_t-1}}{(h_t-1)!} e^{-\alpha u_0}. \quad (1.6)$$

1.4 Linear-quadratic model

The linear-quadratic model considers that a cell contains one single target. This model is based on a radiobiological approach¹: after a radiation dose u_0 , the cell dies either by a single lethal event on the target which is represented by a linear component or by the combination of two sublethal events close enough in time and space, which is represented by a quadratic component.

Thus, the cell death probability after a radiation dose u_0 is defined as

$$q_c = 1 - p_c = 1 - e^{-(\alpha u_0 + \beta u_0^2)}, \quad (1.7)$$

where α and β are two positive parameters.

Dawson and Hillen⁴ provide a detailed explanation using radiation physics and leading to (1.7). Note that the linear quadratic (LQ) model has been gaining popularity these recent years².

However, under the *single-target* assumption, the surviving cell population is homogeneous in terms of radiation injuries in cells. That is why we revisit in this paper the target modeling theory in a stochastic framework able to handle the heterogeneity of damages.

1.5 Multi-target-single-hit models

Here, the cell has m distinct targets and dies when the m targets have been inactivated. Each target can be deactivated by a single hit. According to (1.5), this event occurs with probability $1 - e^{-\alpha u_0}$. Under the assumption that the deactivation of targets are independent events, the probability that the cell dies is

$$q_c = (1 - e^{-\alpha u_0})^m. \quad (1.8)$$

Similarly to the single target models, the variation in cell radio-sensitivity has not been taken into account and all cells have the same survival probability $p_c = 1 - q_c$.

2 Multinomial model of a tumor

Two main aspects of tumor growth are generally missing in the typical hit models: (i) the heterogeneity of damages induced by radiations in the cancer cell population after each dose fraction and (ii) the target reparation between two consecutive dose fractions. Thereafter, we thus propose to take these two issues into account in the multinomial model²⁹. In this section, we detail the multinomial model without the cell proliferation which will be introduced afterward in Section 5.

2.1 Radiation scheduling

We restrict our study to fractionated radiation schedules that have 5 dose fractions per week. More specifically, the first fraction is given on Monday morning, and there is no treatment on the weekends. The treatment is based on a static (i.e. fraction sizes do not vary over time) scheme illustrated in Figure 1 by an impulse train $u(k)$ in which u_0 denotes the magnitude of each dose fraction (typically $u_0 = 2Gy$) and k is the discrete time based on a daily sampling rate. Thus, $d(k) = \sum_{i=0}^k u(i)$ is the cumulated dose of radiation up to time k . The treatment planning process is composed of the following steps:

- the patient image data is acquired, typically fully 3-D Computed Tomography (CT) scans;
- based on this CT scan, the physician outlines the tumor and important normal structures on a computer like the gross target volume, the clinical target volume, and the planning target volume;
- each 3-D CT scan is decomposed into subvolumes called voxels. It is sup-

posed that each voxel v received a uniform dose $u_{0,v}$ per fraction, but the latter may vary from a voxel to another one.

2.2 Heterogeneity of cell states after radiations

We consider that a cell contains m targets. Each target can be made inactive by radiation particules and the cell death occurs when the m targets are deactivated. After a fraction of treatment, a cell may have $m + 1$ possible states:

- state i , the cell has i inactive targets, $i \in \{0, 1, \dots, m - 1\}$, these are the m states of a surviving cell;
- state m , the cell having m inactive targets is a dead cell.

Figure 2 shows the case of a 3-target cell and the corresponding cell states.

2.3 Discrete-time Markov chain model of a cancer cell

A discrete-time Markov chain model is proposed to describe the heterogeneity of cellular damages during the fractionated treatment.

Let us first consider a single cell composed of m targets. Let Z_k be the random variable describing the state of the cell at time k , $Z_k = i \in \{0, 1, \dots, m\}$ is the number of deactivated targets at time k . We suppose that (Z_k) is a discrete-time Markov chain, *i.e.* the cell state at time $k + 1$ only depends on the current state at time k and let Π the corresponding transition matrix. We determine thereafter the expression of Π which models both of effects of dose fractions and repair mechanisms.

2.3.1 Treatment effect modeling.

We adopt the convention that the first row and first column of a matrix will be noted by the index value 0. Denote $\mathbf{P}(i, j)$ the probability to deactivate j targets at time $k+1$ when i targets are disabled at time k . Let q the probability to inactivate a target after a dose fraction u_0 . Moreover, we suppose that the disabling of targets in the cell are independent events. Thus after applying a fraction dose, the possible states at time $k+1$ of a cell in state i at time k are $\{i, i+1, \dots, m\}$. The cell may switch at time $k+1$ to the state j by the deactivation of $j-i$ target(s) among the $m-i$ active ones. Consequently,

$$\mathbf{P}(i, j) = \binom{m-i}{j-i} q^{j-i} (1-q)^{m-j}. \quad (2.1)$$

Then, we obtain the general expression of the matrix \mathbf{P} ,

$$\mathbf{P}(i, j) = \begin{cases} \binom{m-i}{j-i} q^{j-i} (1-q)^{m-j} & i \leq j \\ 0 & j < i \end{cases} \quad (2.2)$$

and the explicit expression is

$$\mathbf{P} = \begin{pmatrix} (1-q)^m & \binom{m}{1} q (1-q)^{m-1} & \dots & q^m \\ 0 & (1-q)^{m-1} & \dots & q^{m-1} \\ \vdots & \vdots & \vdots & \vdots \\ 0 & 0 & \dots & q \\ 0 & 0 & \dots & 1 \end{pmatrix}. \quad (2.3)$$

Figure 3 shows the transition graph of the radiation process before taking the repair of inactive targets into account, for the case of a 3-target cell, *i.e.* $m = 3$.

The target deactivation parameter q is the probability to deactivate an active target after a radiation dose fraction u_0 . To connect this parameter with the real treatment schedule, we consider the following possibilities:

- If we assume that a target is deactivated when it is hit by one or more radiation particles, then according to (1.4), we have

$$q = P(N_h \geq 1) = 1 - e^{-\alpha u_0}, \quad (2.4)$$

where N_h is the random number of radiation particles that hit a given target.

- According to the (LQ) model, recall that after a dose fraction u_0 a cell dies with probability $q_c = 1 - e^{-\alpha u_0 - \beta u_0^2}$. However, it is clear that in our model $q_c = \mathbf{P}(0, m) = q^m$. Consequently,

$$q = (1 - e^{-\alpha u_0 - \beta u_0^2})^{\frac{1}{m}}. \quad (2.5)$$

2.3.2 *Reparation modeling in surviving cells.*

We introduce now repair mechanisms of deactivated targets which occur between the application of two consecutive dose fractions. Let r the probability of an inactive target in a living cell to revive during the period that separates two consecutive dose fractions. We assume that any target can be repaired independently from each other. The possible states at time $k + 1$ of a cell in state i at time k are $\{0, 1, \dots, i\}$. Denote $\mathbf{R}(i, j)$ the probability that the cell

switches at time $k + 1$ to the state j . Since $i - j$ targets among the i inactive targets are repaired, then

$$\mathbf{R}(i, j) = \begin{cases} \binom{i}{j} r^{i-j} (1-r)^j & j \leq i < m \\ 0 & i < j. \end{cases} \quad (2.6)$$

For $i = m$, $\mathbf{R}(m, m) = 1$ and $\mathbf{R}(m, j) = 0$ for all $j \neq m$. The explicit expression is

$$\mathbf{R} = \begin{pmatrix} 1 & 0 & 0 & \dots & 0 \\ r & 1-r & 0 & \dots & 0 \\ r^2 & \binom{2}{1} r(1-r) & (1-r)^2 & \dots & 0 \\ \vdots & \vdots & \vdots & \ddots & \vdots \\ r^{m-1} & \binom{m-1}{1} r^{m-2}(1-r) & \dots & \dots & 0 \\ 0 & 0 & 0 & \dots & 1 \end{pmatrix}. \quad (2.7)$$

2.3.3 Transition matrix of (Z_k) .

We model the dynamics of the Markov chain $(Z_k)_{k \in \mathbf{N}}$ by taking firstly the effects of dose fractions and secondly repair mechanisms into account as follows

$$\Pi = \mathbf{P}\mathbf{R}, \quad (2.8)$$

where \mathbf{P} models the effects of dose fractions, and \mathbf{R} describes repair mechanisms.

In the case of a 3-target cell,

$$\mathbf{\Pi} = \begin{pmatrix} (rq + q')^3 - (rq)^3 & 3r'qq'^2 + 6rr'q^2q' & 3q^2q'r'^2 & q^3 \\ rq'^2 + 2r^2qq' & r'q'^2 + 4rr'qq' & 2r'^2qq' & q^2 \\ r^2q' & 2rr'q' & r'^2q' & q \\ 0 & 0 & 0 & 1 \end{pmatrix} \quad (2.9)$$

where $q' = 1 - q$ and $r' = 1 - r$. Figure 4 shows the transition graph corresponding to the Markov chain (Z_k) after taking the repair of inactive targets into account.

2.3.4 Probability distribution of Z_k .

Set $\nu_k = (\nu_k^0, \dots, \nu_k^m)$ the probability distribution vector of Z_k : $\nu_k^i = P(Z_k = i)$. Using the Markov chain property, ν_k may be expressed in terms of Π and ν_0 :

$$\nu_k = \nu_0 \Pi^k. \quad (2.10)$$

If we assume that the cell is initially in state 0, then $\nu_0 = (1, 0, \dots, 0)$ and

$$\nu_k^i = \Pi^k(0, i) \quad i \in \{0, \dots, m\}. \quad (2.11)$$

2.3.5 Comparison with hit models.

The multi-target–single-hit model is a special case of the multinomial model by considering that all sublethal damages are completely repaired between dose fractions, *i.e.* by taking the repair parameter r equal to 1. Indeed, when $r = 1$, a cell is either dead or in state 0, then the surviving cell population is homogeneous. This and assuming q verifies (2.4) lead to the case of the multi-target–single-hit model.

Similarly, if we fix the target number parameter $m = 1$ and the deactivation target parameter q equals to (2.5), we get the the linear quadratic model.

2.4 Multinomial model of the tumour

Consider a group of n_0 cells that compose the tumour. We divide the tumour into n_t voxels. We suppose that a voxel v of the computerized tomography scan contains n_v cells *i.e.*

$$n_0 = \sum_{v=1}^{n_t} n_v. \quad (2.12)$$

In each voxel v we assume that:

- cells behave independently and with the same dynamics (cf Section 2.3);
- the probability q_v to deactivate a target in a cell is the same for all cells located in v ;
- the probability of target repair r is constant and does not depend on v .

For each cell j , we associate a discrete-time Markov chain $(Z_k^{(j)})$, where $Z_k^{(j)}$ is the random number of deactivated targets. Therefore, the Markov chains $\{(Z_k^{(j)})\}_{j \in \{1, \dots, n_v\}}$ are independent and have the same transition matrix Π_v .

Let $X_{k,v}(i)$ be the random number of cells in state $i \in \{0, \dots, m\}$, at time k , among the n_v initial cells in the voxel v . Since $Z_k^{(1)}, \dots, Z_k^{(n_v)}$ are *i.i.d.*, and follow a categorical distribution, then $(X_{k,v}(0), \dots, X_{k,v}(m))$ follows a multinomial distribution with parameters n_v and $\nu_k = (\nu_k^0, \dots, \nu_k^m)$. Consequently, $Pr(X_{k,v}(0) = h_0, \dots, X_{k,v}(m) = h_m)$, is given by

$$\begin{cases} \frac{n_v!}{h_0! \dots h_m!} (\nu_k^0)^{h_0} \dots (\nu_k^m)^{h_m} & \text{if } \sum_{i=0}^m h_i = n_v \\ 0 & \text{otherwise} \end{cases} \quad (2.13)$$

where $h_i, i \in \{0, \dots, m\}$, are non-negative integers.

Note that the number $X_{k,v}(i)$ of cells in state i at time k follows the binomial distribution:

$$X_{k,v}(i) \sim \mathcal{B}(n_v, \Pi_v^k(0, i)). \quad (2.14)$$

Consequently, its average number is

$$E(X_{k,v}(i)) = n_v \Pi_v^k(0, i). \quad (2.15)$$

2.5 Number of surviving cells

In the *multinomial* model, the number of surviving cells in the voxel v after the k^{th} dose fraction is given by

$$N_{k,v} = X_{k,v}(0) + \dots + X_{k,v}(m-1) = n_v - X_{k,v}(m). \quad (2.16)$$

Since $X_{k,v}(m) \sim \mathcal{B}(n_v, \Pi_v^k(0, m))$, then

$$N_{k,v} \sim \mathcal{B}(n_v, 1 - \Pi_v^k(0, m)). \quad (2.17)$$

This implies that

$$E(N_{k,v}) = n_v(1 - \Pi_v^k(0, m)), \quad (2.18)$$

and

$$Var(N_{k,v}) = n_v(1 - \Pi_v^k(0, m))\Pi_v^k(0, m). \quad (2.19)$$

3 Tumor Control Probability

The probability that no cancer cell remains in a tumor after radiation is known as the Tumor Control Probability (TCP). This probability may be useful to evaluate either the quality of a treatment planning or for its optimization.

Recall that the tumor is decomposed into n_t voxels (cf Section 2.4) and these voxels are supposed to be independent, then the TCP at k is given by

$$TCP_k = \prod_{v=1}^{n_t} VCP_{k,v}, \quad (3.1)$$

where $VCP_{k,v}$ denotes the Voxel Control Probability at time k , *i.e.* the probability of having no cancer cell in the voxel v .

Expressions of VCP

The binomial and Poisson formulations of VCP , for a uniformly irradiated volume v (voxel), are generally used in radiotherapy planning^{30–32}. First, let

$p_{c,v}(k)$ denote the probability that a cancer cell located in the voxel v survives after k dose fractions with magnitude u_0 . Since we have supposed that all cells behave independently, then the number of surviving cancer cells after the k^{th} dose fraction follows a binomial distribution $\mathcal{B}(n_v, p_{c,v}(k))$, and we obtain

$$VCP_{k,v} = (1 - p_{c,v}(k))^{n_v}. \quad (3.2)$$

When the distribution $\mathcal{B}(n_v, p_{c,v}(k))$ may be approximated by the Poisson distribution $\mathcal{P}(n_v p_{c,v}(k))$, we have

$$VCP_{k,v} = e^{-n_v p_{c,v}(k)}. \quad (3.3)$$

The main drawback of hit models presented in Section 1 is to ignore the repair mechanism and the heterogeneous distribution of the cellular damages over the tumor and over time, since $p_{c,v}(k)$ is defined as

$$p_{c,v}(k) = (p_{c,v})^k, \quad (3.4)$$

where $p_{c,v} = p_{c,v}(1)$ is determined by equations (1.5), (1.6), (1.7) and (1.8) according to each model. The above relation (3.4) means that after each dose fraction a surviving cell has the same probability $p_{c,v}$ to survive after the next dose fraction.

However, considering the *multinomial* model presented in Section 2.4, the cell radiation sensitivity increases with the number of dose fraction and for a cell initially in state 0 we have

$$p_{c,v}(k) = 1 - \Pi_v^k(0, m). \quad (3.5)$$

Then, the multinomial VCP at time k is defined according to (3.2) as

$$VCP_{k,v} = \left(\Pi_v^k(0, m) \right)^{n_v}. \quad (3.6)$$

Therefore, according to (3.1) we obtain the TCP for the whole tumour :

$$TCP_k = \prod_{v=1}^{n_t} \left(\Pi_v^k(0, m) \right)^{n_v}. \quad (3.7)$$

4 Normal Tissue Complication Probability

The main undesirable effect due to radiotherapy is the irradiation of normal tissue. Normal organs and tissues have different responses to radiations due to their distinct architecture. Niemierko and Goitein³³ proposed a division of normal tissues into three different architectures: *serial architecture* (*e.g.* nerves or spinal cord), *parallel architecture* (*e.g.* kidney, liver or lung) and *graduated response* (*e.g.* skin or mucous membranes).

We restrict ourselves to the parallel architecture. It is supposed that organs are composed of functional subunits (FSUs) and that organ function is compromised when a certain critical fraction of these FSUs is damaged.

The Normal tissue Voxel Complication Probability, noted $NVCP_{k,v}$, is defined as the probability that a complication appears in a normal tissue voxel v at time k . The Normal Tissue Complication Probability $NTCP_k$ in the whole tissue at time k is the probability that at least one voxel among the \bar{n}_t voxels of the normal tissue has been damaged. If we assume that radiation injury to

voxels are independent events, then

$$NTCP_k = 1 - \prod_{v=1}^{\bar{n}_t} (1 - NVCP_{k,v}). \quad (4.1)$$

For a uniformly irradiated voxel with \bar{n}_v FSUs and a reserve capacity of $(\bar{n} - 1)$ FSUs, it is supposed that^{34,36}:

- a complication appear if the number of damaged FSUs exceeds \bar{n} ;
- each FSU among the \bar{n}_v ones is damaged with a probability p_{FSU} ;
- all FSUs behave independently.

Let N_{FSU} be the random number of damaged FSUs among the \bar{n}_v ones after irradiation, then it has a Binomial distribution $\mathcal{B}(\bar{n}_v, p_{FSU})$ and the probability of complication in the voxel v can be expressed mathematically as

$$NVCP_v = P(N_{FSU} \geq \bar{n}) = \sum_{i=\bar{n}}^{\bar{n}_v} \binom{\bar{n}_v}{i} (p_{FSU})^i (1 - p_{FSU})^{\bar{n}_v - i}. \quad (4.2)$$

Multinomial NVCP

In our model, we suppose that each FSU is one normal cell. Assume that the dynamic of normal cells is similar to the one of cancer cells and given by the multinomial model, defined in Section 2.4, but with different values of the parameters. Then, a normal cell contains \bar{m} targets, each of them is deactivated with a probability \bar{q} and it is repaired with a probability \bar{r} . However, if the treatment plan is correctly designed, radiation doses are lower in the voxels of normal tissue than in the ones of the tumour. As a consequence, the probability

that a radiation particle inactivates a target in a normal cell, is lower than for a cancer cell ($\bar{q} < q$). Moreover, the repair mechanism for normal tissue cells is better for fractionated radiation than tumour cells for reasons which are not yet explained. Consequently, the probability for an inactive target to be reactivated is greater for a normal cell than for a cancer cell ($\bar{r} > r$).

For simplicity, we use the same notation, as for cancer cells, to denote the probability $\bar{\Pi}_v^k(0, \bar{m})$ that a normal cell, located in a voxel v , is in state \bar{m} at time k (dead cell). $\bar{X}_{k,v}(\bar{m})$ is the number of dead cells at time k among the \bar{n}_v initial cells in a normal voxel v . Obviously, $\bar{X}_{k,v}(\bar{m})$ is the analogue of $X_{k,v}(m)$ (cf Section 2.4). Since the complication in the normal voxel v occurs when the dead cell number is larger than \bar{n} , then the $NVCP_v$ expression at time k can be written as

$$NVCP_{k,v} = P(\bar{X}_{k,v}(\bar{m}) \geq \bar{n}) = \sum_{i=\bar{n}}^{\bar{n}_v} \binom{\bar{n}_v}{i} (\bar{\Pi}_v^k(0, \bar{m}))^i (1 - \bar{\Pi}_v^k(0, \bar{m}))^{\bar{n}_v-i}. \quad (4.3)$$

Note that, equation (4.3) is a special case of (4.2) for $p_{FSU} = \bar{\Pi}_v^k(0, \bar{m})$. In particular, if complications only occur when all cells are killed *i.e.* $\bar{n}_v = \bar{n}$, the definitions of NVCP and VCP coincide and the normal voxel complication probability becomes

$$NVCP_{k,v} = (\bar{\Pi}_v^k(0, \bar{m}))^{\bar{n}_v}. \quad (4.4)$$

Finally, integrating (4.3) in (4.1), we obtain the NTCP for the normal tissue in the irradiated zone.

5 Cell proliferation modeling

First let us describe the new behavior of a given cell taking the reproduction phase into account. Once the k^{th} dose fraction is applied, the cell may be damaged, thus repair mechanisms and proliferation follow until the $k+1^{th}$ dose fraction. The damage and repair phases are again modelled as in Section 2.3. We suppose that the cell may reproduce if only it remains in state 0 after the application of a dose fraction, which occurs with a probability $\mathbf{P}(0, 0) = (1 - q)^m$. A cell that stays in state 0, divides and gives birth to two daughter cells in state 0 with probability μ or it remains unchanged with probability $1 - \mu$. It is convenient for our computation, in the case of cell division, to consider the mother cell is still alive and a new one (in state 0) is artificially added.

Consider a voxel v that contains n_v cells in state 0. All cells behave as described previously and independently. Let S_1 be the random number of the additional cells in state 0 resulting from cell reproduction after applying the first dose fraction on the n_v cells. Since a new cell is produced with a probability $\mu(1 - q_v)^m$, then

$$S_1 \sim \mathcal{B}(n_v, \mu(1 - q_v)^m). \quad (5.1)$$

Consequently,

$$\eta_1 := E(S_1) = n_v \mu (1 - q_v)^m. \quad (5.2)$$

The number $X_{1,v}^p(0)$ of cells in state 0, at time $k = 1$, after including the cell proliferation becomes

$$X_{1,v}^p(0) = X_{1,v}(0) + S_1, \quad (5.3)$$

where $X_{1,v}(0)$ is the number of cells in state 0 after the first dose fraction and

the repair phase, among the n_v initial cells,

$$X_{1,v}(0) \sim \mathcal{B}(n_v, \Pi_v(0, 0)).$$

We replace S_1 in the next steps by its mean value $\eta_1 = E(S_1)$ and recall that these new cells are in state 0. We deduce that modeling the treatment effects, repair mechanisms and cell proliferation in the initial cell population of n_v cells is considered to be equivalent to model the treatment effects and repair mechanisms on these cells and to add η_1 cells in state 0. This analysis can be repeated at each time k adding a number η_k of cells in state 0 resulting from cell reproduction. The sequence η_k is given recursively by

$$\left\{ \begin{array}{l} \eta_0 = n_v \\ \eta_{k+1} = \mu(1 - q_v)^m \sum_{j=0}^k \Pi_v^{k-j}(0, 0) \eta_j \quad k \geq 0 \end{array} \right. \quad (5.4)$$

and the new expression of the VCP becomes

$$VCP_{k+1} = \prod_{j=0}^k \left(\Pi_v^{k+1-j}(0, m) \right)^{\eta_j} \quad k \geq 0. \quad (5.5)$$

6 Numerical analysis

6.1 Comparative analysis with typical VCP/NVCP

Recall that we have observed that classical hit models are particular cases of the multinomial model by fixing the target reparation parameter r and \bar{r} for

cancer and normal cells respectively at $r = \bar{r} = 1$ or by taking the *single-target* assumption *i.e.* $m = 1$. Therefore the comparison between VCP/NVCP typical model *vs* VCP/NVCP multinomial model reduces to study the influence of the parameter r (and \bar{r}) on the VCP/NVCP models.

For simplicity we only consider one voxel. The multinomial VCP and NVCP equations (3.6) and (4.3) were implemented in the Matlab environment. The parameters were fixed to $m = 3$, $q_v = 0.7$, $n_v = 10000$ for cancer cells; $\bar{m} = 3$, $\bar{q}_v = 0.6$ and $\bar{n} = \bar{n}_v = 1000$ for normal cells. We chose parameter values avoiding numerical complications so that they permit to obtain numerical results without any specific biological interpretations. The values of the repair parameters for the multinomial VCP/NVCP curves are $r = 0.3$ and $\bar{r} = 0.5$; and recall that $r = \bar{r} = 1$ for the classical VCP/NVCP models. The radiation treatment is decomposed into 50 dose fractions. Note that $VCP_{k,v}$ and $NVCP_{k,v}$ given by (3.6) and (4.3) respectively, are functions of k . In practice, it is more convenient to express them in terms of the cumulated dose $d(k) = ku_0$. Figure 5 presents the VCP/NVCP curves obtained as functions of the cumulated dose d . Blue lines denote the VCP curves; the solid and dashed lines correspond to $r = 0.3$ and $r = 1$ (typical assumption) respectively. Similarly, red curves represent the NVCP with $\bar{r} = 0.5$ (solid line) and $\bar{r} = 1$ (dashed line). For each couple of VCP/NVCP curves, an optimal dose OD is estimated by maximizing the total dose with the constraint $NVCP \leq 0.05$.

The optimal total doses OD1 and OD2 are deduced from the NVCP curves, as

$$OD1 = \max\{d, \text{multinomial } NVCP(d) \leq 0.05\},$$

$$OD2 = \max\{d, \text{typical } NVCP(d) \leq 0.05\}.$$

We observe that the optimal dose $OD2 \approx 46Gy$ derived from the typical VCP/NVCP curves ($r = \bar{r} = 1$) is clearly greater than the optimal dose $OD1 \approx 27Gy$ corresponding to the multinomial VCP/NVCP curves calculated with $r = 0.3$ and $\bar{r} = 0.5$.

The above numerical results show an important difference between the outcome of each couple of the VCP/NVCP curves. This is mainly due to heterogeneity of cell states and reparation process in cancer and normal cells, quantified by the multinomial modeling. As a therapeutical consequence, this approach may reduce the total radiation dose to be delivered and thus the risk of side effects.

6.2 VCP calculation for a clinical schedule

We present here a VCP calculation taking into account the proliferation of cells with a given real value of dose fraction u_0 . The VCP equation (5.5) was implemented in the Matlab environment using for the parameter q the relation (2.5) depending on α and β (1.7). The parameters were fixed to $m = 3$, $r = 0.3$, $\mu = 1$, $n_v = 10000$ and we consider the couple $(\alpha, \beta) = (0.3, 0.03)$ used in³⁵.

Figure 6 displays the variation of the VCP as function of the cumulated dose d . The solid curve represents the VCP function for $u_0 = 1Gy$ and the dashed one corresponds to $u_0 = 2Gy$. This shows the sensitivity of the VCP prediction to the u_0 values. It is expected that the efficiency of the treatment increases with the value of the dose fraction u_0 .

7 Conclusion

In this paper, we proposed a *multinomial* model suited to treatment in radiotherapy, which takes into account (i) the variety of cell responses according to their biological states and (ii) the repair mechanisms that occur between dose fractions. Moreover we included the proliferation of cells that may produce during the treatment period. The radio-sensitivity of cells due to their positions in the cell cycle and the angiogenesis process (tumour blood supply) have not been considered in our model.

The new model is composed of only three parameters: the number m of critical targets which allows to quantify the heterogeneity of intracellular damages during the treatment plan, the probability q for a target to be deactivated by radiation and the probability r for an inactive target in an alive cell to be reactivated. The parameter q is related to the radiation dose u_0 through the intrinsic sensitivity of a target to radiation. Moreover, the multinomial model is a generalization of typical hit models. Based on the multinomial model, new expressions of the TCP and NTCP have been proposed for nonuniform radiations which permits to deduce the optimal total dose to be delivered. We point out the important influence of the repair parameter r which could lead to reduce both the total radiation dose to be delivered and the risk of side effects.

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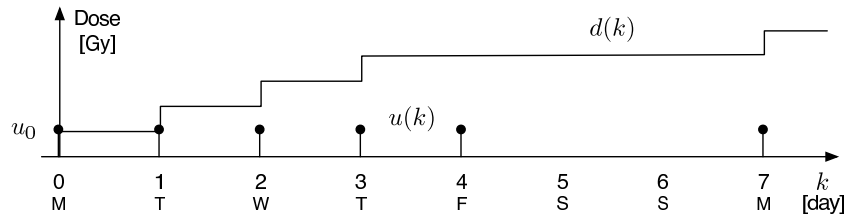


Figure 1. Radiation static scheme: $u(k)$ is an impulse train of dose fractions daily delivered, five days a week; $d(k)$ is the cumulated dose of radiation.

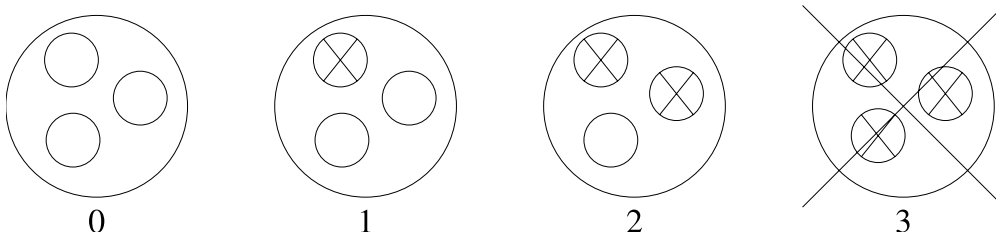


Figure 2. Heterogeneous states of a cell ($m = 3$) after radiation exposure.

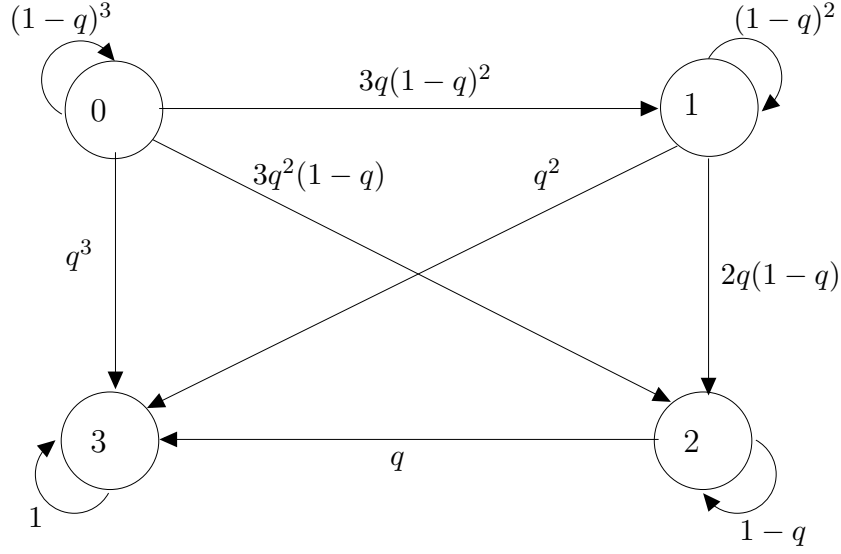


Figure 3. Transition graph of radiation process, with $m = 3$ and before taking target repair mechanisms into account.

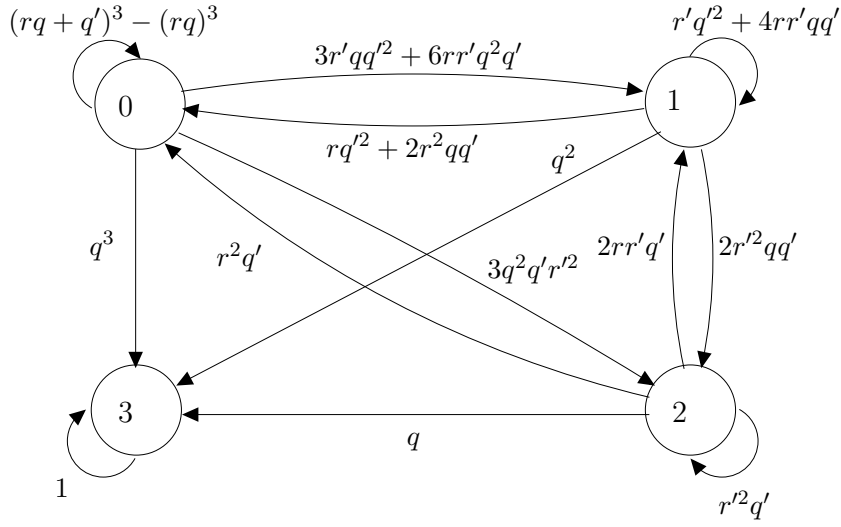


Figure 4. Transition graph of the Markov chain $(Z_k)_{k \in \mathbf{N}}$ where $m = 3$ and after including the repair of inactive targets.

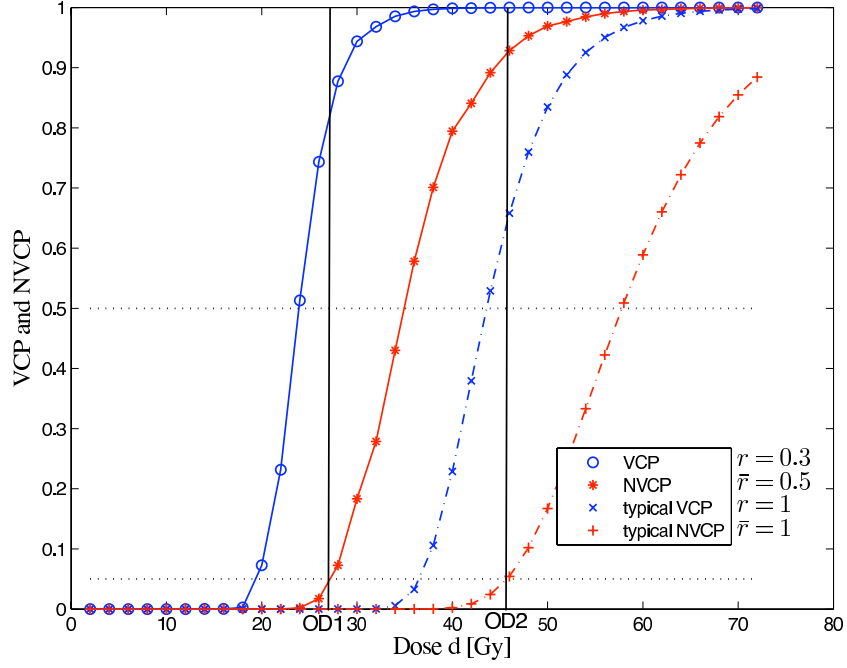


Figure 5. Calculated values of VCP and NVCP as functions of the cumulative dose d . Blue curves represent VCP functions: solid line for $r = 0.3$ and the dashed line for $r = 1$ (typical VCP). Red curves represent the NVCP functions, where $\bar{r} = 0.5$ in solid line and $\bar{r} = 1$ (typical NVCP) in dashed line. For $r = \bar{r} = 1$, the corresponding optimal dose OD2, that maximizes the VCP with the constraint $NVCP \leq 0.05$, is larger than the optimal dose OD1 obtained with the other VCP/NVCP functions.

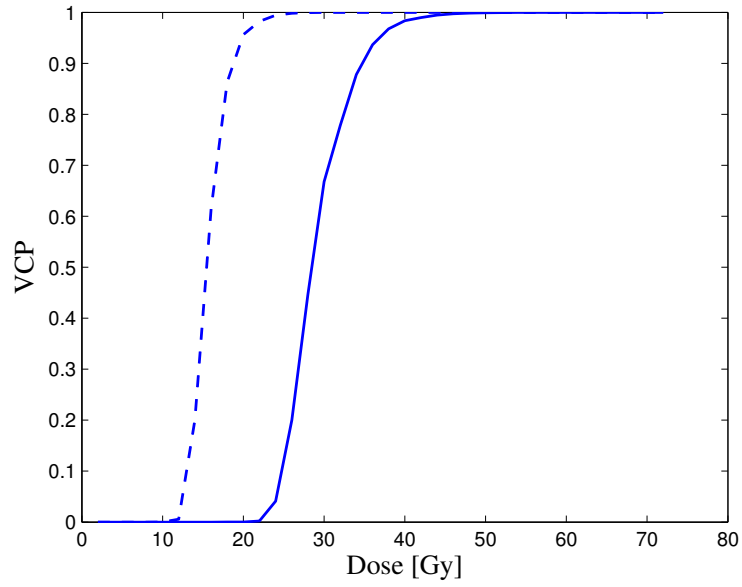


Figure 6. Calculated values of VCP as function of the cumulative dose d taking into account the cell proliferation for the fixed parameters $m = 3$, $r = 0.3$, $\mu = 1$, $n_v = 10000$, $(\alpha, \beta) = (0.3, 0.03)$. The solid curve represents the VCP function for $u_0 = 1Gy$ and the dashed one corresponds to $u_0 = 2Gy$.